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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,617	10/03/2001	Lawrence A. Rheins	DERM1100-3	3610

7590 06/02/2004

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,617	RHEINS ET AL.	
	Examiner	Art Unit	
	Zachary C Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10/03/2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7 are pending in the instant application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

In instant application, the first sentence of the specification claims priority to U.S. Application 09/375609 but there is no statement that the instant application is a divisional of U.S. Application 09/375609.

Drawings

In order to avoid abandonment, the drawing informalities noted in Paper No. 10/31/2001, mailed on 10/31/2001, must now be corrected. Correction can only be effected in the manner set forth in the above noted paper.

Objections

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title "Method for detection of biological factors in the epidermis" is not descriptive because there are no claims directed to methods of detection of biological factors. The claims are all directed to a method of diagnosis of irritant contact dermatitis (ICD) in a subject.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6720145. Although the conflicting claims are not identical, they are not patentably distinct from each other because although the claims differ in scope, the patented claim is narrower than claims 1-7, and the species anticipates the genus of claims 1-7. Claim 1 of the U.S. Patent No. 6720145 is drawn to a method of distinguishing ICD from ACD in skin cells

from a human subject by a step of quantifying IL-4 and IL-8 mRNA, which anticipates claims 1 and 5-7 of the instant application which are drawn to a method of diagnosing ICD in a subject by a step of quantifying IL-4 or IL-8 mRNA, because diagnosing ICD in a subject necessarily entails distinguishing ICD from both normal skin and skin exhibiting ACD, and because both method steps involve quantitation of mRNA encoding IL-4 and IL-8 cytokines. Claims 2 and 3 of the instant application are obvious over claim 1 of U.S. Patent No. 6720145 in further view of Paludan (reference AH cited in the IDS of 4/14/2003), which teaches (in the abstract) PCR, including a hybridization step, as a method of quantitating mRNA encoding IL-8 cytokine. Claim 4 of the instant application is obvious over claim 1 of U.S. Patent No. 6720145 in further view of Paludan and Torrence, US Patent 5,583,032. In paragraph 202, Torrence teaches use of RNase protection assays to detect polynucleotides as an independent and quantitative method to confirm detection of mRNA by a PCR method (RT-PCR).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention 2) state of prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working templates, 6) breadth of claims, 7) amount of direction of guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(a) Claim 1-7 are drawn towards diagnosis of ICD. The only reference point the specification (Table 3) teaches towards diagnosis of ICD is the levels of IL-4 and IL-8 mRNA after 72 hours of exposure to an irritant. In order to diagnose ICD in a subject, it must be determined that the dermatitis is not an ACD reaction. The specification (Table 3) teaches only that the ratios of IL-4 and IL-8 mRNA to GADPH mRNA are different after 72 hours of exposure to an irritant (an ICD reaction) than after 48 hours of exposure to an allergen (an ACD reaction). Applicants do not disclose the quantity of IL-4 and IL-8 mRNA in an ACD reaction at 72 hours. Due to the high level of unpredictability in the art (set forth in the following paragraph), and in the absence of other evidence, it is not predictable what the levels of IL-4 and IL-8 mRNA will be after 72 hours of exposure to an allergen.

The teachings of Kondo (reference AN cited in the IDS of 11/20/2002) indicate that the levels of epidermal cytokine mRNA vary significantly over time following

exposure to an allergen or irritant. In particular, Kondo teaches that in mice, ACD was characterized by an initial suppression in IL-Iα levels followed by an increase in 1L-1α mRNA levels at 12 to 24 hours following exposure to hapten and that IL-1β, IL-6, 1L- 10 and GM-CSF mRNA levels did not increase until 6 hours after exposure to a hapten. In addition, Kondo teaches that in ICD, 1L-1 mRNA levels were upregulated 1 hour following exposure to a hapten, but then were suppressed 3-24 hours following exposure. Furthermore, Kondo teaches that at 24 hours following exposure to a hapten IL-1β, IL-6, IL-I0 and GM-CSF mRNA levels were increased in both ICD and ACD, and thereby levels of these cytokines at 24 hours could not be used to distinguish between ICD and ACD. Kondo teaches (page 372) that it is important to select the appropriate time points and to look at the entire time course of the reaction to elucidate markers to differentiate ACD and ICD. Grangsjo (reference AB cited in the IDS of 6/09/2003) also highlights the unpredictability in the art of detecting the level of cytokine as indicative of response to irritants in that Grangsjo reports that the cytokine response in ICD may be time and substance dependent. Specifically, Grangsjo found that nonanoic acid (NAA), but not SLS induced an increase in IL-6 mRNA levels, whereas SLS, but not NAA, induced an increase in GM-CSF levels.

(b) Claims 1-4 encompass any cell isolated from a subject. These claims are rejected because while they are enabled for detecting mRNA in skin cells, they are not enabled for cells other than skin cells. In the absence of other evidence in the specification, it is not predictable that ICD could be diagnosed by using cells other than skin cells. No working examples are provided in the specification of methods of

diagnosis using cells other than skin cells. What is missing from the specification is a disclosure of the quantity of cytokine mRNAs necessary to diagnosis ICD in cells other than skin cells. It is not predictable that mRNA levels would change in non-affected tissues. To use the instantly claimed method would require undue experimentation to determine in which cell types the quantity of cytokine mRNA present in cells would be indicative of ICD.

(c) Detection of DNA. While the prior art appreciates the detection of RNA, specifically mRNA as an indicator of expression of cytokines (or other proteins), the DNA that is transcribed to make the mRNA would not be expected to be present in any different quantity when the gene is expressed, as opposed to when it is not. It is not accepted in the art that cytokine expression happens via DNA amplification; rather the DNA is transcribed to make mRNA, which is translated to make protein. Amplification (the production of protein in an amount disproportionate to the amount of DNA present) can happen either at the transcription or translation step, and often at both, but not by DNA amplification. Accordingly, since the person of ordinary skill in the art would not accept that DNA levels would be indicative of cytokine expression, and as the specification provides no guidance nor working examples of such, the specification is not enabling of detection of DNA for diagnosis or distinguishment of inflammatory reactions or any other disorder not directly associated with a change in the DNA itself.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in that it recites the acronym ICD (irritant contact dermatitis). Use of acronyms results in indefinite language because the acronyms used to define proteins can be subject to change or reference more than one protein. Therefore, when used for the first time scientific terms should be completely spelled out.

Claim 1 is also indefinite because the recitation "...wherein the amount IL-4 or IL-8 is indicative of ICD..." fails to specify sufficient method steps to allow diagnosis of ICD. It is not clear what amount (including zero) of IL-4 or IL-8 is indicative of skin cells exhibiting an ICD reaction as compared with normal skin cells or skin cells exhibiting an ACD reaction. Applicants teach in Table 3 ratios of IL-8 and IL-4 mRNA to GADPH mRNA which are indicative of ICD and ACD. The claims do not set forth a comparison step in which levels are compared to a control or reference value.

Claim 1 is also indefinite because the recitation "...wherein the amount IL-4 or IL-8 is indicative of ICD..." is unclear as to whether the applicant is referring to the amount of IL-4/IL-8 polynucleotide or protein. In regard to this matter, this claim would be definite if Applicant amended the portion of the claim to read, "...wherein the amount <u>of mRNA encoding</u> IL-4 or IL-8 is indicative of ICD".

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Paludan (reference AH cited in the IDS of 4/14/2003).

Paludan teaches, on page 834, "our technique has proved useful for discriminating between epidermal IL-8 mRNA levels in a variety of inflammatory skin diseases and reactions (Fig 5, Table II). On page 834, Paludan teaches "Screening of more than a hundred epidermal samples showed ... IL-8/GAPDH mRNA ratios varied from 0 in eight normal persons, over low ratios in cases with ... irritatitve patch test reactions (0-0.07)..." The irritative patch test reaction is equivalent to ICD (irritant contact dermatitis). On page 833, Paludan teaches using 3% sodium lauryl sulfate (SLS) to produce the irritative reaction. Application of SLS to skin is well known in the art to induce irritant contact dermatitis. For example, Kondo (reference AN cited in the IDS of 11/20/2002) teaches in the abstract, "Sodium lauryl sulfate (SLS), utilized as an irritant control, was applied to the ears of another group of mice to induce ICD." Also for example, in the instant application, "irritant contact dermatitis (ICD) was induced by applying 0.5% sodium lauryl sulfate (SLS) in distilled water for 72 hours to the upper arm." Therefore, Paludan anticipates a method of diagnosis of ICD by quantifying IL-8 mRNA from skin cells.

With respect to claim 2, Paludan teaches in the abstract "a polymerase chain reaction (PCR) cDNA amplification protocol useful for quantification of specific mRNAs in small skin samples..." and that "we analyzed interleukin 8 mRNA levels..." Therefore, Paludan anticipates using PCR to quantify IL-8 mRNA in order to diagnose ICD.

Claim 3 recites "the method of claim 1, wherein the polynucleotide is detected by hybridization with a polynucleotide probe", which encompasses hybridization with any polynucleotide. Paludan teaches, on page 831, oligonucleotide primers for IL-8 which hybridize with the cDNA copy of the IL-8 mRNA for initiation of PCR. Therefore, Paludan anticipates IL-8 mRNA detection by hybridization with a polynucleotide probe.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan in further view of Asada, et al 1997. As described above, Paludan teaches all of limitations of claim 1 in respect to quantification of IL-8 mRNA. Paludan further teaches, on page 834, that their technique "should be applicable to analysis of other cytokine mRNAs..." Paludan does not teach quantification of a polynucleotide encoding cytokine IL-4 wherein the amount IL-4 is indicative of ICD". Asada teaches, in the abstract, "isolated mRNA from dispase-separated epidermis and dermis of ... naïve BALB/c mice at various times after TNCB challenge. Changes in ... IL-4 mRNA levels (by semiquantitave RT-PCR) were more reproducible and dramatic than those of other cytokines studied." On page 408, Asada teaches that 1% TNCB causes nonspecific inflammatory changes in naïve mice. On page 409, Asada uses the expression "nonspecific (irritant) reactions", indicating the terms are being used equivalently in this reference. The nonspecific inflammatory changes in naive mice do not include a change in IL-4 mRNA (Figure 1A, IL-4 box, -/T columns). A change in IL-4 mRNA is observed in the allergic response observed in sensitized mice (Figure 1A, IL-4 box, T/T columns). Asada shows that IL-4 mRNA is not induced in response to an irritant reaction. In claim 1 of the instant invention, the quantity of IL-4 indicative of ICD is not specified. However, the specification on page 20, paragraph 61 teaches "Figure 1, lane 1 shows the RNA isolated from an ACD erythematous area of skin" and "the band for cytokine IL-4 can be clearly seen in lane 1, but not in lane 3 which contains RNA from ICD cells." Therefore,

the specification teaches diagnosis of ICD based on the absence of IL-4 mRNA (a quantity of zero). This result is anticipated by Asada because they describe an absence of IL-4 mRNA in response to the irritant 1% TNCB. The person of ordinary skill in the art would have been motivated to substitute the quantity of IL-4 mRNA for the quantity of IL-8 mRNA taught by Paludan because, in the absence of other evidence, quantification of IL-4 mRNA would provide as reliable of a diagnosis of ICD as quantification of IL-8 mRNA.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan, 1992 in further view of Torrence, US Patent 5,583,032. As described above, Paludan teaches all of the limitations of claim 1, including detection of a polynucleotide (mRNA) by PCR. Paludan does not teach detecting the polynucleotide by RNase protection assay. In paragraph 202, Torrence teaches use of RNase protection assays to detect polynucleotides as an independent and quantitative method to confirm detection of mRNA by a PCR method (RT-PCR). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute RNase protection assays to detect polynucleotides for the PCR method to detect polynucleotides taught by Paludan. The person of ordinary skill in the art would have been motivated to make that modification because Torrence teaches RNase protection assay as a method to independently confirm quantitative RT-PCR results, and in the absence of any evidence to the contrary, identical results would be expected using this method for IL-8 mRNA.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary L Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER